FPC CONSULTING

43 Emery Avenue, Flemington, New Jersey 08822
Telephone (908) 782-3431 Facsimile (908) 782-2445

1433 '99 MAR 24 A10:11

March 22, 1999

Dockets Management Branch
HFD-305, Room 1-23
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

Dear Sirs:

Enclosed please find a suitability petition herewith submitted to the Food & Drug Administration at the request of our client, Knoll AG.

Please contact me if you have any questions or comments.

Sincerely yours,

Donald P. Cox

Donald P. Cox, Ph.D.
Partner

99P-0673

CP1

Knoll AG

BASF Pharma

knoll

Knoll AG · Postfach 21 08 05 · 67008 Ludwigshafen, Germany

Dockets Management Branch
HFD-305, Room 1-23
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

USA

18th March 1999/yh

Dear Sirs:

This letter authorizes FPC Consulting, Inc., 43 Emery Avenue, Flemington, NJ 08822 to submit on our behalf a petition requesting the filing of an abbreviated new drug application for ibuprofen 200mg tablets.

As our Agent, FPC Consulting is also authorized to respond to any comments or inquiries relating to this petition.

Very truly yours,

ppa. Dr. Biesalski

i. V. Dr. Breitenbach

Knollstraße, 67061 Ludwigshafen · Telefon (06 21) 5 89-0 · Telefax (06 21) 5 89-28 96 · Telex 464823 kn d · Telegramme: Knoll Ludwigshafenrhein
Banken: Deutsche Bank AG, Ludwigshafen, Kto. 0136 796 (BLZ 545 700 94) · Postgiro Ludwigshafen, Kto. 151 671 (BLZ 545 100 67)
Sitz der Gesellschaft: Ludwigshafen/Rhein · Vorsitzender des Aufsichtsrats: Eggert Voscherau · Vorstand: Thorlef Spickschen, Vors.,
Harald Huhn, Erich Schlick, Peter Tonne, Dirk Wuppermann · Amtsgericht Ludwigshafen/Rhein, HRB 4300

Knoll AG · Postfach 21 08 25 · 67008 Ludwigshafen, Germany

Dockets Management Branch
HFD-305, Room 1-23
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

17th March 1999/yh

CITIZEN PETITION

The undersigned submits this petition under section 505 (j)(2)(c) of the Federal Food, Drug and Cosmetic Act and 21CFR314.55(d) to request the Commissioner of the Food and Drug Administration to permit the filing of an ANDA for a drug that has the same active ingredient as an approved drug (NDA No. 20402, approved April 20, 1995) but differs in dosage form.

A. ACTION REQUESTED

By this petition, Knoll AG requests that the Commissioner of the Food and Drug Administration permit the filing of an Abbreviated New Drug Application for ibuprofen 200mg tablets. This drug product differs from the reference product, **PROVEL® Solubilized Ibuprofen Liquicore Capsules,** (NDA No. 20402) which are solubilized ibuprofen capsules, 200mg manufactured by R.P. Scherer and licensed to Sandoz, in that the dosage form is a tablet. The referenced solubilized ibuprofen product is currently marketed as **ADVIL 200mg Liqui-Gels®,** which are manufactured by R.P. Scherer and distributed by Whitehall-Robins Healthcare.

B. STATEMENT OF GROUNDS

Request for listing ibuprofen 200mg tablets in the list of drug products suitable for submission as an ANDA is based on the following justifications:

Knollstraße, 67061 Ludwigshafen · Telefon (0621) 589-0 · Telefax (06 21) 5 89-28 96 · Telex 464823 kn d · Telegramme: Knoll Ludwigshafenrhein
Banken: Deutsche Bank AG, Ludwigshafen, Kto. 0136 796, (BLZ 545 700 94) · Postgiro Ludwigshafen, Kto. 151 671 (BLZ 545 100 67)
Sitz der Gesellschaft: Ludwigshafen/Rhein · Vorsitzender des Aufsichtsrats: Gerhard R. Wolf · Vorstand: Thorlef Spickschen, Vors.,
Erich Schlick, Peter Tonne, Dirk Wuppermann · Amtsgericht Ludwigshafen/Rhein, HRB 1252

17th March 1999

B.1. Comparison with the listed drug:

The proposed ibuprofen 200mg tablets will be identical with the approved drug in all applicable respects, excepting dosage form. For convenient reference, the principal features of the listed drug and the proposed product are compared in the table below:

	Listed Drug	**Proposed Drug**
	Ibuprofen 200mg soft gelatin capsules	Ibuprofen 200mg tablets
1. Conditions of use	Temporarily relieves minor aches & pains	Same
2. Active Ingredient	Ibuprofen	Same
3. Inactive Ingredients	FD&C Green No. 3, Gelatin, Polyethylene Glycol, Potassium Hydroxide, Purified Water, Sorbitan, Sorbitol, Titanium Oxide	Anhydrous Sodium Carbonate, Povidone, Isomaltose, Crospovidone, Colloidal Silicon Dioxide, Propyl Gallate, Purified Water, Film Coating Mixture White 3
4. Strength	200mg	Same
5. Dosage Form	Soft Gelatin Capsule	Tablet
6. Route of Administration	Oral	Oral
7. Labeling	Active Ingredient, Uses, Warnings, Directions, Inactive Ingredients, Storage Conditions	Same as the listed drug, except dosage form, Inactive Ingredients and Storage Conditions
8. Storage Conditions	Store at Room Temperature, but not Above 40C	Store at Room Temperature. But not Above 60C

A copy of the listing from the Approved Drug Products and Legal Requirements, 19th edition, for the discontinued drug product is attached (Appendix I). Also attached are a copy of the package insert labeling for the referenced drug products (Appendix II), and a copy of the proposed product insert labeling (Appendix III)

The proposed product would provide flexibility to the customer and a greater range of storage conditions.

B.2. Supporting bioequivalence study

17th March 1999

A four-way bioequivalence study comparing the test product with three reference products demonstrates substantial equivalence of all products tested. Graphic data from a study report are included (Appendix IV).

C. ENVIRONMENTAL IMPACT

Knoll AG believes the requested action is subject to categorical exclusion under 21CFR25.24(c)(1) and does not require preparation of an environmental assessment.

D. ECONOMIC IMPACT

An analysis will be provided if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Dr. Volker Schwenderemann
Group Vice President
Business Unit Extrusion

Dr. J. Breitenbach
Director, Product and Tech.
Development Extrusion

APPENDIX I

IBUPROFEN POTASSIUM

CAPSULE; ORAL

PROVEL

NOVARTIS	200MG	N020402 001 APR 20, 1995

IDOXURIDINE

OINTMENT; OPHTHALMIC

STOXIL

SMITHKLINE BEECHAM	0.5%	N015868 001

SOLUTION/DROPS; OPHTHALMIC

STOXIL

SMITHKLINE BEECHAM	0.1%	N013934 001

IFOSFAMIDE

INJECTABLE; INJECTION

IFEX

BRISTOL MYERS SQUIBB	1GM/VIAL	N019763 001 DEC 30, 1988
	3GM/VIAL	N019763 002 DEC 30, 1988

IMIPRAMINE HYDROCHLORIDE

TABLET; ORAL

IMIPRAMINE HCL

CHELSEA LABS	10MG	N085875 001
	50MG	N085877 001
	25MG	N085878 001
CIRCA	25MG	N084252 002
	10MG	N085220 001
	50MG	N085221 001
EON	25MG	N084869 002
	50MG	N085133 001
	10MG	N085200 001
LEDERLE	25MG	N086267 001
	50MG	N086268 001
	10MG	N086269 001
ROSEMONT	25MG	N087776 001 FEB 10, 1982
VANGARD	25MG	N087619 001 FEB 09, 1982
	50MG	N087631 001 JAN 04, 1982
	10MG	N088036 001 NOV 03, 1982
WEST WARD	25MG	N088222 001 MAY 26, 1983
	50MG	N088223 001 MAY 26, 1983

JANIMINE

ABBOTT	10MG	N017895 001
	25MG	N017895 002
	50MG	N017895 003

IMIPRAMINE HYDROCHLORIDE *(continued)*

TABLET; ORAL

PRAMINE

ALRA	10MG	N083827 001
	25MG	N083827 002
	50MG	N083827 003

PRESAMINE

RHONE POULENC RORER	25MG	N011836 003
	10MG	N011836 006
	50MG	N011836 007

INDECAINIDE HYDROCHLORIDE

TABLET, EXTENDED RELEASE; ORAL

DECABID

LILLY	EQ 50MG BASE	N019693 001 DEC 29, 1989
	EQ 75MG BASE	N019693 002 DEC 29, 1989
+	EQ 100MG BASE	N019693 003 DEC 29, 1989

INDOCYANINE GREEN

INJECTABLE; INJECTION

CARDIO-GREEN

AKORN	10MG/VIAL	N011525 003
	40MG/VIAL	N011525 004

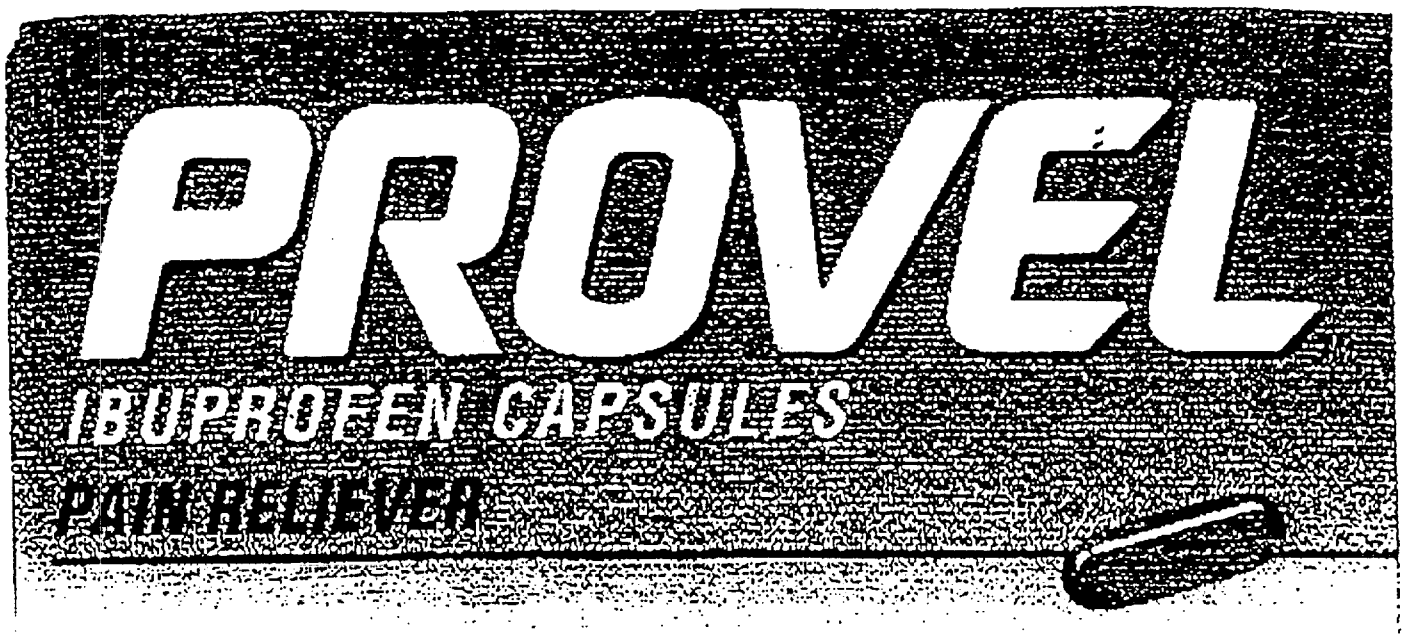
INDOMETHACIN

CAPSULE; ORAL

INDOMETHACIN

BARR	25MG	N070067 001 OCT 03, 1986
	50MG	N070068 001 OCT 03, 1986
CHELSEA LABS	25MG	N018690 001 JUL 31, 1984
	50MG	N018690 002 JUL 31, 1984
	50MG	N071635 001 MAY 18, 1987
CIRCA	25MG	N070784 001 AUG 20, 1986
	50MG	N070785 001 AUG 20, 1986
DURAMED	25MG	N070326 001 OCT 18, 1985
	50MG	N070327 001 OCT 18, 1985
HALSEY	50MG	N070635 001 JUN 03, 1987
	25MG	N070782 001 JUN 03, 1987

APPENDIX II



40 ***Liquicore***™ *Capsules 200 mg*

PROVEL™ *Liquicore™ Capsules 200 mg* PAIN RELIEVER

WARNING: ASPIRIN SENSITIVE PATIENTS. Do not take this product if you have had a severe allergic reaction to aspirin, e.g.- asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin.

Indications: For the temporary relief of pain associated with headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps, for minor aches and pains associated with the common cold, and for reduction of fever.

Directions: Adults: Take 1 Liquicore capsule every 4 to 6 hours while symptoms persist. If pain or fever do not respond to 1 Liquicore capsule, 2 capsules may be used, but do not exceed 6 capsules in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. Children: Do not give this product to children under 12 except under the advice and supervision of a doctor.

Active Ingredient: Each Provel capsule contains Ibuprofen equivalent to 200 mg Ibuprofen USP.

Inactive Ingredients: Gelatin, Green No. 3, Polyethylene Glycol, Potassium Hydroxide, Purified Water, Sorbitol, and other Ingredients.

WARNINGS: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur or if the painful area is red or swollen, consult a doctor. These could be signs of serious illness. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin or acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take this product without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with these except under a doctor's direction. Do not combine this product with any other ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Store at controlled room temperature, 15°-30°C (59°-86°F)

(Continued From Front)

Advil®

SOLUBILIZED IBUPROFEN CAPSULES, 200 mg

Warnings: (continued)

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. **IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.**

Keep out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center right away.

Directions:

Adults:

1. Take 1 capsule every 4 to 6 hours while symptoms persist.
2. If pain or fever does not respond to 1 capsule, 2 capsules may be used, but do not exceed 6 capsules in 24 hours, unless directed by a doctor.
3. The smallest effective dose should be used.

Children: Do not give to children under 12 unless directed by a doctor.

Inactive Ingredients: FD&C Green No. 3, Gelatin, Polyethylene Glycol, Potassium Hydroxide, Purified Water, Sorbitan, Sorbitol, Titanium Oxide.

Store at room temperature 59-86°F (15-30°C). Avoid excessive heat 104°F (40°C).

If You Have Any Questions Or Comments, Please Call 1-800-88-ADVIL

Dist. by: WHITEHALL-ROBINS HEALTHCARE
Madison, NJ 07940 Made in U.S.A.

U.S. Patent Nos. 5,071,643
5,360,615
By arrangement with R.P. Scherer Corp.
Liqui-Gels® is a trademark of R. P. Scherer Corp.
0169-20/15

CONSUMER LABELING LEAFLET FOR ADVIL LIQUI-GELS®

READ THE LABEL Read all product information before using.
Keep leaflet for important information.

Advil®

SOLUBILIZED IBUPROFEN CAPSULES, 200 mg

Active Ingredient (in each green oblong capsule):	**Purpose:**
Solubilized ibuprofen equal to 200 mg ibuprofen (present as the free acid and potassium salt)	Pain Reliever/Fever Reducer

Uses: Temporarily relieves minor aches and pains associated with:

- Common Cold
- Backache
- Headache
- Minor Pain of Arthritis
- Toothache
- Menstrual Cramps
- Muscular Aches

Temporarily reduces fever

Warnings:

Allergy Alert: If, after taking a pain reliever or fever reducer, you have ever had:

• Hives • Facial Swelling • Asthma • Shock

Do not take Advil. You may have a serious reaction.

Alcohol Warning: If you generally consume 3 or more alcohol-containing drinks a day, you should consult your physician for advice on when and how you should take Advil Liqui-Gels® or other pain relievers.

Do Not Use:

- With any other pain reliever/fever reducer
- With any other product containing ibuprofen
- For more than 3 days for fever
- For more than 10 days for pain

Ask a Doctor Before Use If:

- The painful area is red or swollen
- You take other drugs on a regular basis
- You are under a doctor's care for any continuing medical condition
- You have had problems or side effects with any pain reliever/fever reducer

Stop Using This Product and Ask a Doctor If:

- Symptoms continue or worsen
- Stomach pain occurs with use of this product
- Any new or unexpected symptoms occur

(Warnings continued on back)

CONSUMER LABELING LEAFLET FOR **TRADEMARK®**

Read all product information before using
Keep leaflet for important information.

TRADEMARK®

SOLUBILIZED IBUPROFEN TABLETS, 200 mg

Active Ingredient (in each white oblong tablet):	**Purpose:**
Solubilized ibuprofen equal to 200 mg ibuprofen (present a the free acid and sodium salt)	Pain Reliever/Fever Reducer

Uses: Temporarily relieves minor aches and pains associated with:

- Common Cold
- Headache
- Toothache
- Muscular Aches
- Backache
- Minor Pain of Arthritis
- Menstrual Cramps

Temporarily reduces fever

Warnings:

Allergy Alert: If, after taking a pain reliever or fever reducer, you have ever had:

- Hives
- Facial Swelling
- Asthma
- Shock

Do not take TRADEMARK®. You may have a serious reaction.

Alcohol Warning: If you generally consume 3 or more alcohol-containing drinks a day, you should consult your physician for advice on when and how you should take **TRADEMARK®** or other pain relievers.

Do Not Use:

- With any other pain reliever/fever reducer
- With any other product containing ibuprofen
- For more than 3 days for fever
- For more than 10 days for pain

Ask a Doctor Before Use If:

- You are on a sodium-restricted diet
- The painful area is red or swollen
- You take drugs on a regular basis
- You are under a doctor's care for any continuing medical condition
- You have had problems or side effects with any pain reliever/ fever reducer

Stop Using This Product and Ask a Doctor if:

- Symptoms continue or worsen
- Stomach pain occurs with sue of this product
- Any new or unexpected symptoms occur

(Warnings continued on back)

(Continued from Front)

TRADEMARK®

SOLUBILIZED IBUPROFEN TABLETS, 200 mg

Warnings: (continued)

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

Keep our of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center right away.

Directions:

Adults:

1. Take 1 tablet every 4 to 6 hours while symptoms persist.
2. If pain or fever does not respond to 1 tablet, 2 tablets may be used, but do not exceed 6 tablets in 24 hours, unless directed by a doctor.
3. The smallest effective dose should be used.

Children: Do not give to children under 12 unless directed by a doctor.

Inactive Ingredients: Anhydrous sodium carbonate, povidone, isomalt, crospovidone, silicon dioxide, propylgallate, sodium stearyl fumarate, purified water.

Store at room temperature 59-86°F(15-30°C).

☎If You Have Any Questions Or Comments
Please Call 1-800-XXX-XXXX

XXXXXXXXXXXXXXX

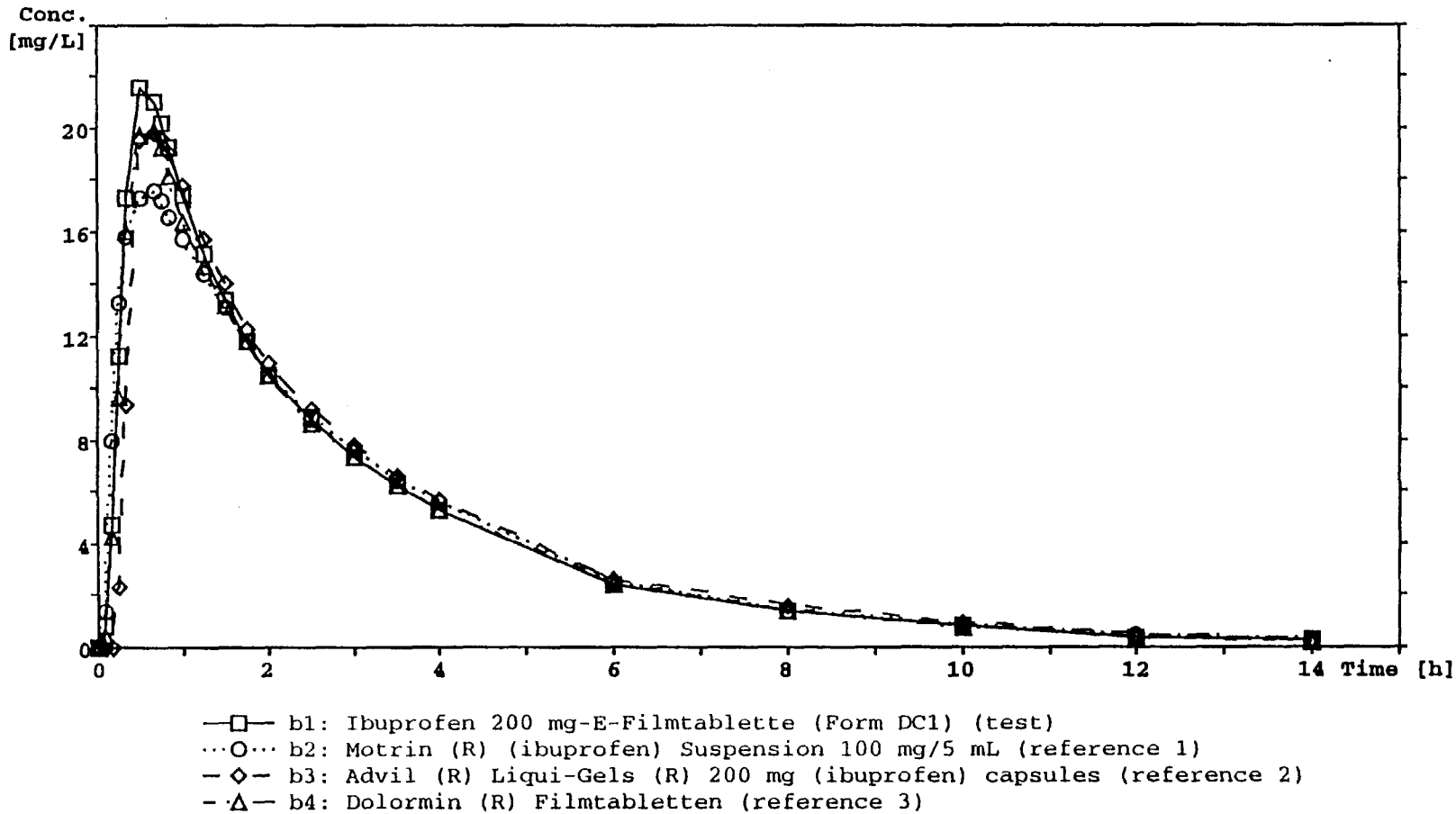


Figure 1

Synoptic plot of geometric mean concentrations of ibuprofen [mg/L] vs time [h] (N=24).

Geometric mean not calculated if less than 1/2 of the individual concentrations are >= 0.22.
Leading not calculated geometric means set to 0. Concentrations < 0.22 calculated as 0.11.

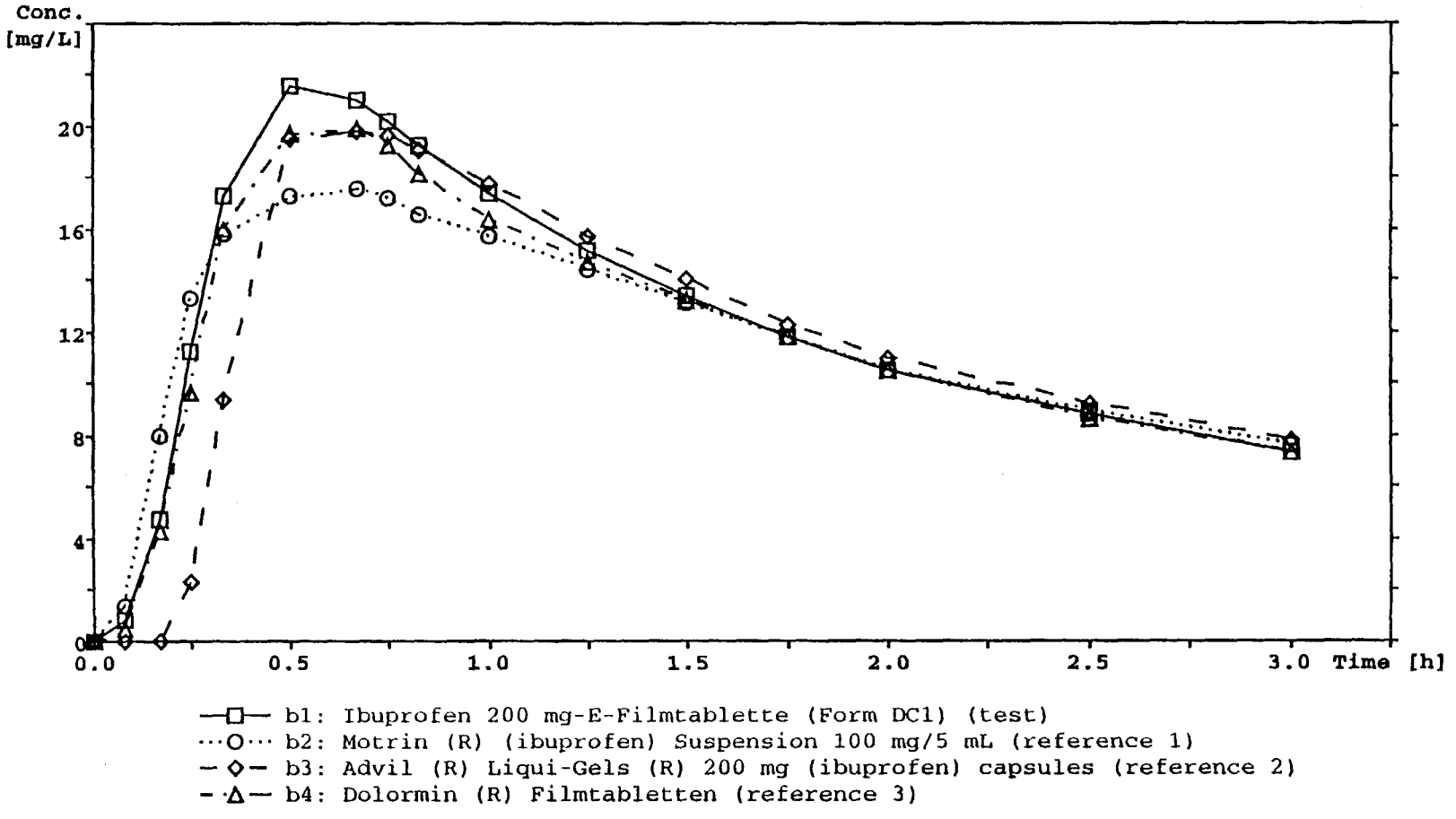


Figure 2

Synoptic plot of geometric mean concentrations of ibuprofen [mg/L] vs time [h] (0-3 h, N=24).

Geometric mean not calculated if less than 1/2 of the individual concentrations are >= 0.22.
Leading not calculated geometric means set to 0. Concentrations < 0.22 calculated as 0.11.

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Company FLEMINGTON PHARMACEUTICAL CORP

Address 43 EMERY AVE FL 2 Dept./Floor/Suite/Room

City FLEMINGTON State NJ ZIP 08822

2 Your Internal Billing Reference Information ANDA SUIT. PETITION - 1.8U.

3 To

Recipient's Name DOCKETS MANAGEMENT BRANCH Phone ( )

Company FOOD & DRUG ADMINISTRATION HFD-305, Room 1-23

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☐ FedEx Express Saver (Third business day)

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4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas

☐ FedEx Overnight Freight (Next business day)

☐ FedEx 2Day Freight (Second business day)

☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging

☒ FedEx Letter ☐ FedEx Pak ☐ FedEx Box ☐ FedEx Tube ☐ Other Pkg.

Declared value limit $500.

6 Special Handling (One box must be checked)

Does this shipment contain dangerous goods?* ☐ No ☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 _____ x _____ kg.

☐ Cargo Aircraft Only

*Dangerous Goods cannot be shipped in FedEx packaging.

7 Payment

☐ Obtain Recipient FedEx Account No.

Bill to: ☒ Sender (Account No. in Section 1 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check

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Total Packages	Total Weight	Total Declared Value*	Total Charges
		$ .00	$

* When declaring a value higher than $100 per shipment, you pay an additional charge. See **SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY** section for further information.

Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

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